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33,383-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No. : 09/806,370 Confirmation No.: 8568

Appellant : Holmes et al.

Filed : October 3, 2001

TC/A.U. : 1645

Examiner : V. Portner

Docket No. : 33,383-00

Customer No. : 38199

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22323-1450

BRIEF ON APPEAL

Sir:

This Appeal Brief is timely filed. A Notice of Appeal was filed by facsimile at the US Patent and Trademark Office on June 29, 2005. The appeal is from the Office Action dated May 9, 2005 and made final, which rejected pending claims 1-11, 13-17, 28-37, and 39-44.

The fee of $500.00 for filing this Appeal Brief is attached hereto. The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account Number 08-3040.

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I. Real party in interest

The real parties in interest are Appellants' assignees:

Wyeth Holdings Corporation located at Five Giralda Farms, Madison, New Jersey, 07940 (Wyeth Holdings Corporation is the successor-in-interest to originally-named assignee, American Cyanamid Company); and

The United States of America as represented by the Uniformed Services University of Health Sciences located at 4301 Jones Bridge Road, F. Edward Hebert School of Medicine, Bethesda, Maryland, 20814-4799.

II. Related appeals and interferences

None.

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III. Status of claims

The pending claims are 1-11, 13-17, 28-37, and 39-44. Claims 1-2, 4-11, 13-17, 28, 30-37, and 39-43 stand rejected. Claim 29 is objected to, but was indicated to be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 3 and 44 are found allowable. Claims 12, 18-27, and 38 have been canceled. Claims 17, 43, and 44 are linking claims.

Claims 1-2, 4-11, 13-17, 28, 30-37, and 39-43 are the subject of this appeal.

IV. Status of amendments

There are no outstanding amendments.

V. Summary of claimed subject matter

Appellants' invention as presented in the claims is drawn to an antigenic composition that includes at least one antigen from a pathogenic organism selected from among a bacterium, a virus, a fungus and a parasite (page 9, lines 20-25 and original claim 1). The composition also includes an effective adjuvanting amount of a mutant cholera holotoxin (page 9, line 25-26 and original claim 1). The mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin (page 9, lines 26-27 and original claim 1) and has a substitution which replaces the glutamic acid (Glu) which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin with an amino acid other than aspartic acid (page 9, lines 28-30 and original claim 1). One example of such an amino acid substitution includes replacing the Glu with a histidine (page 9, lines 30-31 and original claim 3). The mutant holotoxin enhances the immune response in a vertebrate host to the antigen (page 9, lines 20-22). Methods for preparing these antigenic compositions of the invention are also provided (page 4, lines 5-17).

The invention also includes methods for increasing the ability of an antigenic composition containing at least one antigen from a pathogenic organism selected from among a bacterium, a virus, a fungus or a parasite and the mutant cholera holotoxin described above to elicit the immune response of a vertebrate host (page 4, lines 18-28 and original claim 17). The method thereby includes administering the above-described antigenic composition to the host (page 39, lines 1-3 and original claim 17).

VI. Grounds of rejection to be reviewed on appeal

The issues on appeal are the following:

(i) whether the examiner's rejection of claims 1-2, 4, 6-8, 11, 13-17, 28, 30, 32-34, 37, and 39-43 under the provision of 35 USC § 102(b) over Rappuoli et al., International Patent Publication No. WO 95/17211 (hereinafter Rappuoli) as allegedly evidenced by Zhang et al., J. Mol. Biol., 251: 564, 1994 (hereinafter Zhang) should be reversed; and

(ii) whether the examiner's rejection of claims 1, 2, and 13 under the provision of 35 USC § 102(b) over Glineur et al., Infection and Immunity, 62(10):4176, 1994 (hereinafter Glineur) should be reversed.

VII. Argument

(i) *Claims 1-2, 4, 6-8, 11, 13-17, 28, 30, 32-34, 38, and 39-43 are rejected under 35 USC § 102(b) over Rappuoli et al. (International Patent Publication No. WO 95/17211) as allegedly evidenced by Zhang et al. (J. Mol. Biol., 251: 564, 1994).*

The Examiner asserted that Rappuoli discusses a mutant cholera holotoxin where the mutation is a deletion at position 7, which would result in a substitution of tyrosine at position 29 as allegedly evidenced by Zhang which asserts that upon deletion of position 7, the tyrosine at position 30 would become position 29.

Appellants respectfully request reconsideration and withdrawal of this rejection in view of following remarks.

Appellants' Claims have an Unambiguous Meaning

It is only through a tortured misinterpretation of Appellants' claims that the Examiner can arrive at her grounds for rejection. Appellants respectfully submit that their claims have an unambiguous meaning and, therefore, the Examiner's grounds for rejection are baseless.

Appellants' invention is drawn to an antigenic composition including (a) at least one antigen from a pathogenic organism selected from among a bacterium, a virus, a fungus and a parasite; and (b) an effective adjuvanting amount of a mutant cholera holotoxin. As recited in Claim 1, the mutant cholera holotoxin has a **substitution** which ***replaces*** the glutamic acid (Glu) which naturally occurs at position 29 of the A subunit (CT-A) of the **wild-type** cholera holotoxin with an amino acid other than aspartic acid (Asp). The mutant holotoxin thereby has reduced toxicity compared to wild-type cholera holotoxin and also enhances the immune response in a vertebrate host to the antigen.

Neither Claim 1 nor any of the other pending claims recite a **deletion** of one or more amino acids. The skilled person understands that there is a significant difference between a **substitution** and a **deletion** of an amino acid. In a **substitution** (also known as a point mutation; see page 4, lines 2-3 of the specification), there is no

change in the number of amino acids in the protein. By contrast, a **deletion** necessarily reduces the number of amino acids in the protein. It is significant that the words "delete" and "deletion" do not appear anywhere in Appellants' specification or claims. This is entirely consistent with Appellants' position set forth in this Appeal Brief.

The pending claims are clear that the mutant cholera holotoxins contain an amino acid (other than Asp) that **substitutes** for the naturally-occurring Glu that occurs at wild-type cholera holotoxin subunit A position 29. The term **substitution** as used in the claims, noted throughout the specification, and as exemplified by the Examples, clearly refers to the insertion of an amino acid other than Asp in place of Glu in the CT-A. The specification makes clear that by having a **substitution** at position 29, the mutant cholera holotoxin subunit A of Appellants' invention no longer contains the naturally-occurring Glu that was present at position 29 in the wild-type cholera holotoxin subunit A. The specification explicitly teaches that the Glu is replaced by another amino acid. This is specifically supported by the specification and the examples.

For instance, Example 1 describes in detail that each of the cholera holotoxin subunit A mutants was prepared by replacing the indicated amino acid from the cholera holotoxin subunit A sequence with another amino acid in place thereof. For example, in one embodiment, Example 1 specifically describes that the Glu at position 29 is replaced with a His. This is indicated by the designation "E29H", which would readily be understood by those skilled in the art as representing a **substitution** and not a **deletion** of the Glu at position 29. Appellants emphasize that no amino acids were deleted from any other section of the sequence. Only the amino acid at position 29 was changed.

The specification of the present application does ***not*** explicitly or inherently teach that the term "substitution" can include the arbitrary deletion of any of the amino acids at positions 1-28, thereby resulting in a shift of amino acids to provide an amino acid other than Glu or Asp at position 29, with the original Glu at position 29

now occupying another position in the mutant cholera holotoxin subunit A. In fact, such a teaching would be contrary to the intended definition of "substitution" at that site because all of the amino acids in the cholera holotoxin sequence subsequent to the deletion would shift.

It is further noted that the specification and pending claims of the present application are clear in their recitation that the amino acid residues discussed are those of the wild-type cholera holotoxin sequence. It is well known in the art that all of the known variants of cholera holotoxin subunit A have a Glu at their naturally-occurring (or wild-type) residue position 29. Mekalanos *et al*, **1983** *Nature*, 306:551-557 is the standard reference in the art for the well-known sequence of wild-type cholera toxin and its subunits.[1] Such sequences are also available in the NCBI database, as submitted by the authors of the above-noted publication. Thus, in publications throughout the art, a reference to position 29 of wild-type cholera holotoxin subunit A is understood by those of skill in the art to mean the Glu at position 29 in the well-known sequence of subunit A cited in Mekalanos.[2]

Thus, the claims as presently pending are clear and unambiguous in meaning. As is well understood by those of skill in the art, claims "...must be read in view of the specification, of which they are a part".[3] "It is therefore entirely appropriate...to rely heavily on the written description for guidance as to the meaning of the claims".[4] Further, "[o]ne of the best ways to teach a person of ordinary skill in the art how to make and use the invention is to provide an example of how to practice the

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1 See, the "Bibliography entry 1" on page 2, lines 3-4 and the first citation on page 114, labeled "Bibliography" in the Appellants' specification.

2 Note that in a variety of publications, the same convention for identifying amino acid positions of cholera toxin subunit A is used, i.e., by identifying the amino acid by position number with reference to the Mekalanos publication. See, e.g., International Patent Publication Nos. WO 97/02348 and WO 97/29771 and background references cited therein; and Vadheim K.L, et al, 1994 Microb. Pathog., 17(5):339-46.

3 Markman v. Westview Instruments, Inc., 52 F.3d at 967, 978 (Fed. Cir. 1995).

4 Phillips v. AWH Corporation, Fed. Cir., No. 03-1269, July 12, 2005.

invention...".[5] The specification including the examples clearly supports Appellants' interpretation of the claims.

The Documents Cited by the Examiner in the Present Rejection Do Not Teach a Mutant Cholera Toxin (CT) as Described By the Pending Claims.

Zhang is only relied upon by the Examiner for providing the sequences, and comparison thereof, of wild-type cholera toxin (CT) and wild-type *E. coli* heat labile toxin (LT) in Figure 1 of page 564. Appellants do not dispute this point. In fact, Zhang further supports Appellants' assertion that all known CT sequences have a Glu at wild type position 29 by illustrating that position 29 of each toxin described in Zhang has a Glu at that position.

Rappuoli refers to immunogenic compositions containing an immunologically effective amount of an antigen and a mucosal adjuvant. The Examiner asserted that Rappuoli discusses "...a mutant...cholera holotoxin...wherein the mutation is a ***deletion*** mutation at position 7...which would result in a substitution of tyrosine at position 29..." and shows a "...tyrosine at position 30, which would become position 29, upon ***deletion*** of position 7" (emphasis added).[6] The Examiner thus considers Appellants' claims to read on Rappuoli's mutant CT.

Appellants respectfully disagree with the Examiner on this point. Rappuoli only lists ***deletion*** mutants as a ***generic*** option in the description of a detoxified mutant as "optionally comprising one or more amino acid additions, deletions or substitutions"[7] Rappuoli contains no example at all of a cholera holotoxin (CT) or *E. coli* toxin (LT) which is a deletion mutant. The only example of a detoxified mutant provided by Rappuoli involves a ***substitution*** of LT, not CT. Indeed, the only specific mutation of LT taught in Rappuoli is LTK7 (no specific mutations of CT

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5 Ibid.

6 Page 3, paragraph 3 of the March 10, 2004 Office Action

7 See, Rappuoli at page 5, lines 35-38, and page 7, lines 25-28.

were taught). Contrary to the Examiner's assertion that LTK7 is a **deletion** of the residue at amino acid position 7, Rappuoli states at page 6, lines 2-4:

> "For example, a mutant LT in accordance with the invention may possess an Arg7 to Lys7 **substitution** at position 7 of the A subunit, the so-called LTK7 mutant." (Emphasis added)

See also Table 1 at page 14 of Rappuoli.

The Examiner further asserts that Claims 3 and 4 of Rappuoli recite the **deletion** of arginine at position 7. In fact, Claims 3 and 4 merely recite "a mutant of CT or LT" [Claim 3] and "one or more amino acid additions, deletions **or** substitutions in the A subunit of the holotoxin" [Claim 4] (emphasis added). Claims 3 and 4 are utterly silent about any specific change to any specific amino acid position, much less amino acid position 7. Rather, it is Claim 5 of Rappuoli that deals with position 7, and that recitation is specific to LTK7. As discussed above, LTK7 represents the **substitution** of Lysine for Arginine, and not the **deletion** of Arginine at position 7.

However, even if the Examiner were correct in her reading of Rappuoli, such a reading still would not anticipate Appellants' claims, because a deletion of the amino acid at position 7 (or the deletion of one or more amino acids anywhere within positions 1-28) of wild-type CT is not within the scope of Appellants' pending claims. The arbitrary deletion of the amino acid at position 7 of the A subunit of the LT sequence, nowhere specifically disclosed in Rappuoli, would result in the naturally-occurring Glu at wild-type position 29 being shifted, rather than replaced by a substituted amino acid.

Nowhere in Rappuoli is there any reference to a mutant cholera holotoxin subunit A where the naturally-occurring Glu that occurs at wild-type CT-A position 29 is substituted, i.e., replaced with another amino acid. The specification of the present application clearly requires that the naturally occurring Glu at wild-type position 29 be replaced, not simply moved to a different position in the sequence by virtue of an amino acid deletion of any of the amino acid residues in wild-type positions 1-28. Therefore, the Glu at position 29 is no longer present in the claimed

mutant cholera holotoxin sequence. Nor is the Glu at position 29 in the wild-type sequence located at positions 28 or 30, among other positions, of the mutant cholera holotoxin sequence. Consequently, Rappuoli's specific amino acid ***substitution*** at position 7 of LT, or Rappuoli's ***generic*** disclosure of a deletion at an unspecified amino acid position, in combination with the teachings of Zhang results in a mutant LT that is entirely different than the mutant cholera holotoxin of Appellants' invention.

Therefore, Rappuoli alone or taken with Zhang does not anticipate the claims of the present invention.

In view of the above remarks, this rejection may be properly withdrawn.

(ii) *Claims 1, 2, and 13 are rejected under 35 USC § 102(b) over Glineur et al. (Infection and Immunity, 62(10):4176, 1994).*

The Examiner asserted that Glineur discloses an antigenic composition that comprises a mutant holotoxin of cholera toxin with a tyrosine substituted at position 29.

Appellants respectfully request reconsideration and withdrawal of this rejection in view of the following remarks.

Glineur does not anticipate the claims of the present invention because Glineur does not teach an antigenic composition in which a mutant cholera holotoxin is used as an adjuvant for another antigen. Glineur does not anticipate the claims of the present invention because Glineur does not teach the mutant cholera holotoxin described in Appellants' claims.

Glineur Does Not Teach an Antigenic Composition in which a Mutant Cholera Holotoxin is used as an Adjuvant for Another Antigen

Glineur does not teach an antigenic composition which contains a first antigen and a mutant cholera holotoxin (CTX) that has an "adjuvant" effect on the first antigen. Glineur is simply a study of the enzymatic effects of CTX and mutants thereof on certain cell membrane proteins. Glineur teaches that small amounts of

purified CTX, or supernatants from toxin-producing *V. cholerae* cultures, induce morphological changes in four cell membrane proteins of a rat pheochromocytoma clonal (PC12) cell line. These ribosylation effects are believed to be responsible for the efflux of fluids and ions from target cells in diarrhea associated with *V. cholerae* infection.[8]

The CTX and mutant CTX of Glineur were expressed recombinantly in *V. cholerae* cells transformed with a plasmid containing the CTX coding sequence downstream of a tac promoter.[9] The filtered culture medium of *V. cholerae* was then added to cultures of PC12 cells, and the morphological changes observed. The CTX mutants were observed for any effects on the ADP-ribosylation enzymatic activity on membrane-bound proteins.

Glineur refers to only two CTX mutations:

(1) the E29Δ **deletion** mutant having an amino acid ***deletion*** at amino acid position 29; and

(2) the E29D **substitution** mutant in which the naturally occurring glutamic acid at amino acid position 29 in the cholera holotoxin subunit A is **substituted** with the ***most conservative*** amino acid replacement for glutamic acid, i.e., aspartic acid.

The E29Δ deletion mutant had quite different activity from the E29D mutant:

> "[D]eletion of Glu-29 drastically diminished the enzymatic activity of CTX. In contrast, replacement of Glu-29 by Asp had no significant effect on the ADP-ribosyltransferase activity." (Page 4181, col. 2 and Table 1.)

The authors concluded that this PC12 system is useful for testing toxinogenicity of *V. cholerae* isolates and the neutralizing effects of anti-CTX antisera or potency of vaccine candidates. The authors were silent on whether the E29Δ deletion mutant could be useful as an adjuvant. In any event, deletion mutants

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[8] See, for example, Glineur page 4176, col. 2; page 4178, col. 2.

[9] See Glineur page 4179, col. 2 through page 4180.

are **not** the subject of Appellants' claims. The substitution mutant E29D would not be useful as an adjuvant, because it had the enzymatic activity of the wild-type CTX.

The sentence spanning pages 4183 and 4184 (quoted in footnote 10 below) evidences Glineur's lack of teaching the use of any CTX as an adjuvant in an antigenic composition with *another* protein; instead, Glineur commented on its use as an antigen in a cholera vaccine.[10]

Glineur does not teach an antigenic composition containing a first antigen and an adjuvanting amount of a mutant cholera holotoxin adjuvant, and cannot anticipate the invention of the claims.

Glineur Does Not Teach the Mutant Cholera Holotoxin Mutant Described in Appellants' Claims

As noted above, Glineur's teachings related to cholera toxin mutants are limited to the deletion mutant E29Δ and the substitution mutant E29D. Glineur does not teach anything about any other amino acid **substitution** at position 29. Glineur does not teach that a replacement of amino acid position 29 with an amino acid ***other than Asp*** would provide a cholera toxin mutant with the properties necessary (including reduced toxicity) for use as an adjuvant in an antigenic composition. Note that Glineur's E29D had the enzymatic activity of the wild-type CTX. It is only Appellants' disclosure that provides the teaching and support for successful use of an amino acid **substitution *other than Asp*** at position E29 to create a mutant cholera holotoxin useful as an adjuvant in an antigenic composition.

Glineur's deletion mutant is **not** the subject of Appellants' claims.

Further, for the reasons stated above with respect to Rappuoli, the **deletion** of any of the amino acids prior to the naturally-occurring Glu at wild-type CT-A position 29 would shift the specified wild-type Glu residue to another position in the

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[10] "Whatever the exact functional role of Glu-29 may be, the construction of a CTX-CRM with drastically decreased enzymatic and biologically activities represents an interesting possibility for the development of cholera vaccines."

sequence. However, Appellants' invention is not such a mutant. The pending claims require an amino acid **substitution *other than Asp*** in place of the naturally-occurring Glu that is located at position 29 in ***wild-type cholera holotoxin subunit A***. Glineur in no way teaches this requirement of the pending claims. Thus, Glineur does not anticipate the invention of the amended claims.

In view of the above remarks, this rejection may be properly withdrawn.

The Examiner's Citation of US Pat. 5,925,546 Actually Supports Appellants' Position

The Examiner stated at paragraph 17 of the final Office Action:

> "The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Pat. 5,925,546 (Pizza) is cited to show a mutant cholera holotoxin."

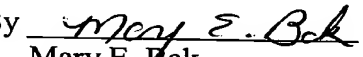
Appellants note first that Pizza is directed solely to mutants of pertussis toxin, rather than to cholera toxin. More importantly, Pizza was granted claims of the same type as those sought here, namely, claims which recited substitutions at specific amino acid positions. Pizza was also not directed to deletions of one or more amino acids. The same rationale which resulted in the issuance of the claims in Pizza should apply to Appellants' claims, and should result in the issuance of Appellants' claims.

Appellants have demonstrated that the claimed subject matter of this application is novel over the cited documents. Appellants thereby request reversal of the outstanding 35 USC § 102(b) rejections for the reasons set forth herein.

Reversal of the examiner's rejection of the claims under appeal (claims 1-2, 4-11, 13-17, 28, 30-37, and 39-43) is requested.

Respectfully submitted,

HOWSON AND HOWSON
Attorneys for Appellants

By 
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VIII. Claims Appendix

Claim 1(Previously Presented): An antigenic composition comprising

(a) at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus and a parasite; and

(b) an effective adjuvanting amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin, and has a substitution which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin with an amino acid other than aspartic acid, and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said antigen.

Claim 2 (Previously Presented): The antigenic composition of Claim 1 wherein the antigenic composition comprises more than one antigen of (a).

Claim 3(Previously Presented): An antigenic composition comprising

(a) at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus and a parasite; and

(b) an effective adjuvanting amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin, and has a histidine which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said antigen.

Claim 4(Previously Presented): The antigenic composition of Claim 1 wherein the antigen is selected from the group consisting of the *Haemophilus influenzae* P4 outer membrane protein, the *Haemophilus influenzae* P6 outer membrane protein, the *Haemophilus influenzae* adherence and penetration protein (Hap_s), the *Helicobacter pylori* urease protein, the *Neisseria meningitidis* Group B recombinant class 1 pilin (rpilin), the *Neisseria meningitidis* Group B class 1 outer membrane protein (PorA),

the respiratory syncytial virus fusion protein, a rotavirus virus-like particle and the herpes simplex virus (HSV) type 2 glycoprotein D (gD2).

Claim 5(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is selected from the group consisting of the *Haemophilus influenzae* P4 outer membrane protein, the *Haemophilus influenzae* P6 outer membrane protein, the *Haemophilus influenzae* Hap_s protein, and any combination thereof.

Claim 6(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is the *Helicobacter pylori* urease protein.

Claim 7(Previously Presented): The antigenic composition of Claim 4 the antigen is selected from the group consisting of the *Neisseria meningitidis* rpilin, *Neisseria meningitidis* PorA protein and any combination thereof.

Claim 8(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is the respiratory syncytial virus fusion protein.

Claim 9(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is a rotavirus virus-like particle.

Claim 10(Original): The antigenic composition of Claim 9 wherein the virus-like particle is a rotavirus 2/6-virus-like particle.

Claim 11(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is HSV gD2.

Claim 12(Canceled)

Claim 13(Original): The antigenic composition of Claim 1 wherein the antigenic composition further comprises a diluent or carrier.

Claim 14(Original): The antigenic composition of Claim 1 which further comprises a second adjuvant in addition to the mutant cholera holotoxin.

Claim 15(Previously Presented): The antigenic composition of Claim 1, wherein at least one additional mutation is made to the A subunit of the mutant cholera holotoxin at a position other than wild-type amino acid position 29, wherein said mutant holotoxin with said additional mutation enhances the immune response in a vertebrate host to said antigen.

Claim 16(Previously Presented): The antigenic composition of Claim 15 wherein the at least one additional mutation is made as a substitution for a naturally-occurring amino acid at an amino acid position of wild-type cholera holotoxin selected from the group consisting of the arginine at amino acid 7, the aspartic acid at position 9, the arginine at position 11, the histidine at position 44, the valine at position 53, the arginine at position 54, the serine at position 61, the serine at position 63, the histidine at position 70, the valine at position 97, the tyrosine at position 104, the proline at position 106, the histidine at position 107, the serine at position 109, the glutamic acid at position 100, the glutamic acid at position 112, the serine at position 114, the tryptophan at position 127, the arginine at position 146 and the arginine at position 192.

Claim 17(Previously Presented): A method for increasing the ability of an antigenic composition containing at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus or a parasite to elicit the immune response of a vertebrate host, which comprises administering to said host an antigenic composition of Claim 1.

Claims 18-27(Canceled)

Claim 28 (Previously Presented): The method of Claim 17 wherein the antigenic composition comprises more than one antigen.

Claim 29(Previously Presented): The method of Claim 17 wherein the amino acid substituted at wild-type position 29 is histidine.

Claim 30(Previously Presented): The method of Claim 17 wherein the antigen is selected from the group consisting of the *Haemophilus influenzae* P4 outer membrane protein, the *Haemophilus influenzae* P6 outer membrane protein, the *Haemophilus influenzae* Hap_s protein, the *Helicobacter pylori* urease protein, the *Neisseria meningitidis* rpilin, the *Neisseria meningitidis* PorA protein, the respiratory syncytial virus fusion protein, a rotavirus, virus-like particle and HSV gD2.

Claim 31(Previously Presented): The method of Claim 30 wherein at least one antigen is selected from the group consisting of the *Haemophilus influenzae* P4 outer membrane protein, the *Haemophilus influenzae* P6 outer membrane protein, the *Haemophilus influenzae* Hap_s protein, and any combination thereof.

Claim 32(Previously Presented): The method of Claim 30 wherein the antigen is the *Helicobacter pylori* urease protein.

Claim 33(Previously Presented): The method of Claim 30 wherein at least one antigen is selected from the group consisting of the *Neisseria meningitidis* rpilin, *Neisseria meningitidis* PorA protein and any combination thereof.

Claim 34(Previously Presented): The method of Claim 30 wherein the antigen is the respiratory syncytial virus fusion protein.

Claim 35(Previously Presented): The method of Claim 30 wherein the antigen is a rotavirus virus-like particle.

Claim 36(Original): The method of Claim 35 wherein the virus-like particle is a rotavirus 2/6-virus-like particle.

Claim 37(Previously Presented): The method of Claim 30 wherein the antigen is HSV gD2.

Claim 38(Canceled)

Claim 39(Original): The method of Claim 17 wherein the antigenic composition further comprises a diluent or carrier.

Claim 40(Original): The method of Claim 17 wherein the antigenic composition further comprises a second adjuvant in addition to the mutant cholera holotoxin.

Claim 41(Previously Presented): The method of Claim 17 wherein at least one additional mutation is made to the A subunit of the mutant cholera holotoxin at a position other than said wild-type amino acid position 29, wherein said mutant holotoxin with said additional mutation enhances the immune response in a vertebrate host to said antigen.

Claim 42(Previously Presented): The method of Claim 41 wherein the at least one additional mutation is made as a substitution for a naturally-occurring amino acid of wild-type cholera holotoxin selected from the group consisting of the arginine at amino acid 7, the aspartic acid at position 9, the arginine at position 11, the histidine at position 44, the valine at position 53, the arginine at position 54, the serine at position 61, the serine at position 63, the histidine at position 70, the valine at position

97, the tyrosine at position 104, the proline at position 106, the histidine at position 107, the serine at position 109, the glutamic acid at position 100, the glutamic acid at position 112, the serine at position 114, the tryptophan at position 127, the arginine at position 146 and the arginine at position 192.

Claim 43(Previously Presented): A method of preparing an antigenic composition comprising combining

(a) at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus and a parasite; and

(b) an effective adjuvanting amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin and has a substitution which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin with an amino acid other than aspartic acid, and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said antigen.

Claim 44(Previously Presented): A method for increasing the ability of an antigenic composition containing at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus or a parasite to elicit the immune response of a vertebrate host, which comprises administering to said host an antigenic composition of Claim 3.

IX. Evidence Appendix

Attached hereto is a copy of the Declaration filed by Appellants on July 12, 2004.

X. Related Proceedings Appendix

None

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